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Method of creating 3D models of small caliber cerebral arteries basing on anatomical specimens

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ABSTRACT

The cerebral circulation is a common site of vascular lesions and concurrent hemodynamic accidents, which often lead to serious neurological disabilities. Recent advances in understanding pathogenesis, improving diagnostics and developing new treatment methods for these conditions result from an interdisciplinary approach to the problem – linking clinical sciences, basic medical sciences and hemodynamical analyses. Most common techniques used in such studies include computational fluid dynamics, which allows for development of 3D models of cerebral vasculature, basing on radiological studies. However, these methods remain flawed, mainly because of their spatial resolution, which is not high enough to visualize the smallest arterial branches (perforating branches) in the models. That leaves the perforators (<1.0 mm) out of most of the contemporary studies, whilst their clinical importance is widely recognized in clinical practice. Obstruction of these vessels by atherosclerotic plaques, thrombi or implantation of flow diverting stents may result in neurological complications such as paralysis or coma. Our research team has recently developed a new method of creating 3D models of the cerebral arterial system based on anatomical specimens and micro computed tomography (micro-CT). We have infused fresh brainstem vasculature specimens with contrast medium, subsequently scanned them using an industrial-grade micro-CT system and finally, created spatial models, which included branches of diameter less than 0.1 mm. None of the current methods have been able to produce models of detail as high as this, which allows us to presume, that our procedure may open up new opportunities for hemodynamical studies within cerebral circulation and beyond.

1. Introduction

Using hemodynamical analyses to solve medical problems has provided ground-breaking findings (Koskinas et al., 2012; Stone et al., 2003). One of the most extensively studied part of cardiovascular system is cerebral circulation (Meng et al., 2014; Staarmann et al., 2019). Describing interactions between blood flow and arterial walls is getting us closer to explaining the development of various diseases, such as atherothrombosis, stroke, aneurysms as well as helps us improve treatment methods.

Studies on hemodynamics use several research methods, with computational fluid dynamics (CFD) being the most popular one (Li et al., 2018). Experimental studies can be also conducted (Li et al., 2020). Every research method begins with obtaining a three-dimensional (3D) model of arteries, usually based on results of standard radiologic studies (digital subtractive angiography (DSA), computed tomography angiography (CTA) or magnetic resonance imaging angiography (MRA)). The precision of constructed models is limited by resolution of aforementioned imaging techniques, ranging between 0.25 and 0.625 mm (depending on the technique and device) (Hallscheidt et al., 2003; Naidich, 2013; Osborn et al., 2018; Schenk et al., 2006; White et al., 2001), making spatial reconstruction of small blood vessels difficult. Therefore, several recent studies could not achieve their objectives of investigating hemodynamics of small diameter arteries. Despite the intent of studying such vessels, the authors did not analyse arteries of diameter lesser than 1.0 mm (Hu et al., 2015; Mazur

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et al., 2016; Wu et al., 2019). However, studying hemodynamics of these arteries is necessary since their malfunction (including those resulting from implantation of flow diverting stents) leads to severe neurological complications (coma, blindness, paralysis and so on) (Brinjikji Waleed et al., 2013; Kulcsár et al., 2010; Phillips et al., 2012; Rajah et al., 2017). Such studies give insight into modelling conditions of pathological flow in those arteries, which are a source of devastating ischemic and haemorrhagic strokes.

The authors developed a method of obtaining reliable 3D models of cerebral arteries from the perforating arteries level to the microcirculation level with a resolution of 0.003 mm, which is presented in this paper.

2. Materials and methods

The model is based on the arterial geometry of anatomical specimens. We present the preparation process of models of distal internal carotid artery (with initial segments of anterior cerebral artery and middle cerebral artery) and basilar artery, because of the clinical significance of its small branches (so-called perforating arteries). The preparation of the model consisted of three main stages (Fig. 1).

All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by The Ethics Committee of Medical University of Warsaw, Poland (Number 138/2020).

2.1. *Step one: Preparation of the specimen*

Firstly, an unfixed brain specimen was obtained from a cadaver. Relevant clinical data was obtained in each case (age, sex, history and histological signs of vascular and neurological diseases, date and cause of death). The cadavers were stored in the temperature of 4–8 °C for up to 5 days; the specimens were stored in the same temperature in the 0.9% NaCl solution for up to 48 h. Only undamaged specimens underwent further steps of preparation. Overall, 23 specimens were included in the study, coming from 11 cadavers (9 male, 2 female). Age at the moment of death ranged from 18 to 69. The basal part of the specimen (12 cm × 12 cm × 5 cm block, basal surface of the brain along with the brainstem) was sufficient to visualise the desired vasculature. The arteries were rinsed clean of any residue using a thin catheter and a standard 20.0 ml syringe filled with 0,9% NaCl solution. The distal branches of the investigated arteries (M2 segments of the middle cerebral artery, A2 segment of the anterior cerebral artery, one of the vertebral arteries, both posterior cerebral arteries and both superior and anterior inferior cerebellar arteries) were ligated. At the same time, the contrast medium was prepared by melting together gelatine solution and barium sulphate (Barium sulfuricum 1.0 g/ml, Medana) in the proportion 1:1 in 60.0 °C water bath. The specimen was placed under the microscope, then the catheter was introduced into the one unligated vessel (either one of the vertebral arteries or internal cerebral artery trunk) and a ligature was loosely tied around the artery. The contrast medium was subsequently drawn into a standard 10.0 ml syringe with a PVC cannula. After that, the medium was infused; standard manual infusion was maintained in the physiological pressures (until it reached 150 mmHg) and performed under visual control without distortion of visible vessels. Distal parts of perforators were covered by parenchyma which additionally protect from distortion. After about 30 s, cold water (15°-20 °C) was poured over the specimen in order to prevent any contrast leaks and solidify the barium-gelatine mixture. When all of the arteries were infused with the medium, the whole specimen was placed in buffered 10% formalin solution and was left to fix for 14 days.

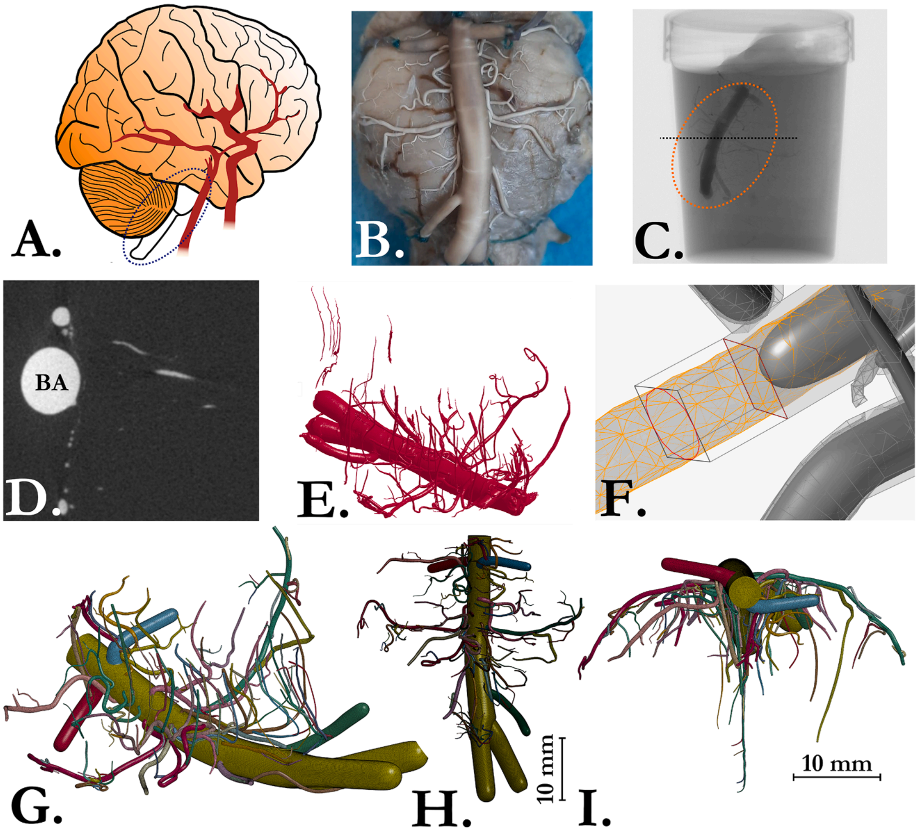

Fig. 1. Steps of creating an accurate geometric model of vessels of diameter below 1 mm on the example of brainstem blood supply (basilar artery and its small branches). **A** Schematic lateral view of human brain. The basilar artery lies on the brainstem (encircled area), in the midline. **B** Anatomical specimen of the brainstem with basilar artery (BA) and its small branches filled with contrast. The specimen was obtained from the cadaver of 40 years old man, without history or histological signs of vascular or neurological diseases. **C** Lateral X-ray scan of the specimen. **D** Axial micro computed tomography (CT) slice of the specimen. The plane of the slice was marked on the lateral X-ray (**C**). BA – basilar artery. **E** STL model created on the basis of micro-CT scan. **F** Polynurbs surface development in the Altaire Inspire system. **G – I** Isometric (**G**), posterior (**H**) and axial (**I**) view of the geometric model of the basilar artery and its small branches. Scale bars represent 10 mm.

2.2. Step two: Imaging with computed micro tomography

Specimens prepared in the aforementioned way were transferred to a lab in the Military University of Technology and scanned with an industrial grade computed tomography system (Nikon/Metris XT H 225 ST). It is a CT scanner equipped with a detector capable of a resolution of 4 million pixels. The specimen rotation was performed using a 5-axis computer-controlled table. An Open Tube UltraFocus Reflection Target radiation source with a maximum resolution of approximately 1 μm was used. Before the imaging, the block was cut into three pieces and each of the arteries was scanned separately. A 0.5 mm thick copper filter was used as filter material to increase the contrast between the sample and the air. The sample was x-rayed to obtain a single voxel size of 3.4 μm. The resolution magnitude is due to the fact that when wishing to perform an x-ray of a higher order than 1 μm, the imaging area is significantly reduced.

2.3. Step three: Creating spatial model of arteries

The images were stored in a DICOM (Digital Imaging and Communications in Medicine) format as a series of x-ray images assigned to a specific axis of the device (tomograph). These images are monochromatic, and the individual shades of grey correspond to the respective radiological density values of the Hounsfield scale. Image processing was performed with CT Pro 3D software (Metris XT 2.2, Nikon Metrology, Belmont, CA). In this program, the individual shades of grey were separated by plotting their Hounsfield values on a histogram. The vessel's fill volume is approximately in the range of 13000 ÷ 18000. The model was then exported as a set of three-node elements forming its surface. The model prepared this way was then cleaned in Altair Hyper Mesh software. The final geometry was developed by extracting surfaces based on the ".stl" model using the poliNURBS surfaces available in the Altair Inspire system. This gives great applicability in the flexible and precise description of both analytical shapes described by mathematical formulae and modelled shapes. The model was then re-imported into Altair HyperMesh where discretisation was performed resulting in a shell model (Interactive 3D Model).

3. Discussion

The paper presents a method for 3D models development of small cerebral arteries and perforating branches of major cerebral arteries. By using micro tomography, it was possible not only to visualise the presence of small arteries, but also to precisely reconstruct their course. This is crucial for using the models in hemodynamic studies such as CFD. The anatomical specimens were chosen as a base for the model, due to certain limitations which are related to the examination of living tissues. Possibilities of the used micro CT raises hope to also visualise the level of microcirculation in future investigations. Based on the resulting model, a flow domain will be developed to verify the nature of the flow in perforators, as described before (Tomaszewski et al., 2020; Tomaszewski et al., 2020). The created geometries of cerebral arteries will be uploaded to an open-access repository.

The resolution of standard CT is insufficient, making performing a computed micro tomography scan on a living person's brain unfeasible, as it would require the use of an immense amount of ionizing radiation in order to achieve resolution high enough to visualise the smallest of the arteries (Goldman, 2007). Obviously, that would be harmful for the examined person.

That limitation does not apply to other imaging methods, such as magnetic resonance imaging (MRI), but in both of these imaging methods the examined tissue has to be properly immobilized during the procedure if the resolution is to be high enough (Chandarana et al., 2018). This problem has disqualified the 7 T MRI as our method of choice, as achieving satisfying resolution of the image was impossible due to the live brain itself pulsating and the need for the examined person to not move at all for a prolonged time. Recent studies on 7 T MRI of cerebral circulation did not provided as accurate images as needed to reconstruct the course of small arteries (less than1.0 mm) (De Cocker et al., 2018; Harteveld et al., 2015).

The method presented in this paper is fairly simple, reliable and cost-effective, which makes it applicable for modelling the small vasculature of any other organ of the human body. The procedures for other organs (e. g. kidney, thyroid) would have to be slightly adjusted to accommodate their specific vascularisation. Nevertheless, the general idea and procedure would remain unaltered, delivering the researchers a proper model.

Another strength of the presented method is the possibility of studying the histopathology of the reconstructed arteries. The specimens were conserved with buffered 10% formalin solution, therefore histological slides can be prepared. This opens the unique and valuable possibility of analysing hemodynamics and response of walls of the same artery, allowing drawing inferences about clinical significance of detected patterns of blood flow. Such information is almost always unavailable when obtaining 3D models of vessel tree from living patient. Concurrently, as not the whole brain has to be scanned to visualize the perforating arteries, desired samples of the tissue (e.g. the post-communicating segments of posterior cerebral arteries) can be obtained before fixation and utilized to determine its mechanical properties, which can be used for the geometric model in mathematical modelling. Alternatively, in the next steps an indirect method can be adopted, as described previously (Mazurkiewicz et al., 2021).

The method presented has also several limitations. First is the lack of follow-up. However, it allows analysing response of arterial walls to different flow patterns by taking advantage of the histological studies in return. The second is the lack of information about boundary conditions, which have to be estimated on the basis of other studies and medical history (age, sex, history of hypertension etc.). Noteworthy, non-invasive methods (namely Doppler ultrasonography) can only measure the flow patterns and pressure in vertebral and internal carotid arteries (sometimes also in middle cerebral artery). These parameters cannot be measured at distal ending of studied models (including posterior cerebral artery and branches of middle cerebral artery). Furthermore, there is no method of measuring pressure of blood in arteries with diameters lesser than 1.00 mm.

CRediT authorship contribution statement

Radosław Rzepliński: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Michał Tomaszewski:** Methodology, Software, Formal analysis, Data curation, Writing - original draft. **Mikołaj Sługocki:** Methodology, Investigation, Writing - original draft. **Krzysztof Karczewski:** Investigation, Resources, Writing - review & editing. **Paweł Krajewski:** Investigation, Resources, Writing - review & editing. **Tymon Skadorwa:** Investigation, Formal analysis, Writing - review & editing. **Jerzy Małachowski:** Methodology, Writing - review & editing, Supervision, Funding acquisition. **Bogdan Ciszek:** Methodology, Resources, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Interactive 3D Model. The geometry of the basilar artery and its branches, including perforating arteries. The basilar artery lies on the brainstem and supplies it with blood. The perforating arteries form 90-degree angle with parent vessels and penetrate nervous tissue. Obstruction of these vessels by atherosclerotic plaques, thrombi or implantation of flow diverting stents may result in severe neurological complications such as paralysis or coma. Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbiomech.2021.110590.

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